Remarks

Claims 1-9 and 11 were pending. By this amendment, claim 3 is cancelled. Due to the restriction requirement, claims 5-9 and 11 are withdrawn. No claims are added. Therefore, claims 1-2 and 4 are now pending.

35 U.S.C. § 112, first paragraph

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph, on the ground they do not satisfy the enablement requirement. It is asserted that the specification fails to present any evidence or sound scientific reasoning to support a conclusion that N-type calcium channel is specifically associated with depression or that depression is regulated by N-type calcium channel activity. Applicants disagree and request reconsideration.

To determine if the N-type calcium channel is involved in depression, the inventors subjected N-type calcium channel knock-out mice to behavioral tests used by those in the art as to screen for anti-depression agents. It is not relevant whether the mouse used is an art-recognized model for depression. Instead what is relevant is whether the assays used are art recognized assays for depression. Behavior tests, including the forced swimming test (see Porsolt *et al.*, *Eur. J. Pharmacol.* 51:291-4, 1978, Exhibit A) and the tail suspension test (Steru *et al.*, *Psychopharmacol.* 85:367-70, 1985, Exhibit B) are accepted behavior tests in the art that can be used to screen for anti-depression agents.

The results in the application demonstrate that N-type calcium channel relates to depression, and that depression can be alleviated by blocking N-type calcium channel activity (as modeled using a mouse knockout of the alpha 1B subunit of the N-type calcium channel). For example, as shown in Figure 3 and discussed in Example 2.1 (pages 25-26), in the forced swimming test, the knock-out mice swam for the entire 15 minute testing period, while normal mice stopped swimming after about 5 minutes. In addition, as shown in Figure 4 and discussed in Example 2.2 (pages 26-27), in the tail suspension test, the knock-out mice had a significantly decreased immobilization time, as compared to normal mice. Based on these *in vivo* results, one skilled in the art would conclude that reducing or inhibiting N-type calcium channel activity (e.g. by mimicking the knock-out mice) can reduce depression.

Further evidence that the N-type calcium channel activity is involved in depression is provided in Iga *et al.* (*Neurosci. Lett.* 400:203-7, 2006, Exhibit C). This article reports that LIM

(PDLIM5) interacts with protein kinase C-epsilon and N-type calcium channel alpha-1B subunit and modulates neuronal calcium signaling in involved in major depression.

Therefore, the specification is fully enabled for the scope of the claims, and Applicants request that the 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Double patenting

Applicants were notified that if claim 1 was found to be allowable, claim 3 would be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 1. Applicants have cancelled claim 3. Therefore, there is no longer a potential double-patenting issue.

If there are any questions or minor issues to be resolved before a Notice of Allowance is granted, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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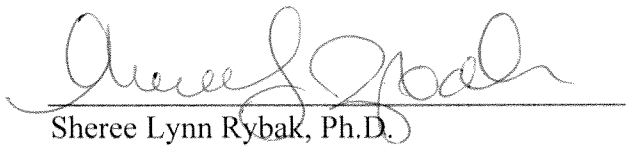
By 
Sheree Lynn Rybak, Ph.D.
Registration No. 47,913

1: Eur J Pharmacol. 1978 Oct 1;51(3):291-4.

"Behavioural despair" in rats and mice: strain differences and the effects of imipramine.

Porsolt RD, Bertin A, Jalfre M.

Rats and mice when forced to swim in a restricted space will rapidly cease attempts to escape and become immobile. Previous experiments have shown that immobility was selectively reduced by antidepressant agents. The present experiments show that important differences exist between strains in both the amount of immobility observed and the effects of imipramine. Strain differences should therefore be taken into account in attempts to replicate results from one laboratory to another.

PMID: 568552 [PubMed - indexed for MEDLINE]

Related Links

Non-specificity of "behavioral despair" as an animal model of depression. [Eur J Pharmacol. 1979]

Individual differences in response to imipramine in the mouse tail suspension test. [Psychopharmacology (Berl). 1997]

The immobility response in the forced swim test: paradoxical effect of imipramine. [Eur J Pharmacol. 1994]

Influence of imipramine on the duration of immobility in chronic forced-swim-stressed rats. [Acta Med Okayama. 2004]

Learned immobility explains the behavior of rats in the forced swimming test. [Physiol Behav. 1989]

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EXHIBIT A: PAGE 1 OF 1

1: Psychopharmacology (Berl). 1985;85(3):367-70.

Links

The tail suspension test: a new method for screening antidepressants in mice.

Steru L, Chermat R, Thierry B, Simon P.

A novel test procedure for antidepressants was designed in which a mouse is suspended by the tail from a lever, the movements of the animal being recorded. The total duration of the test (6 min) can be divided into periods of agitation and immobility. Several psychotropic drugs were studied: amphetamine, amitriptyline, atropine, desipramine, mianserin, nomifensine and viloxazine. Antidepressant drugs decrease the duration of immobility, as do psychostimulants and atropine. If coupled with measurement of locomotor activity in different conditions, the test can separate the locomotor stimulant doses from antidepressant doses. Diazepam increases the duration of immobility. The main advantages of this procedure are the use of a simple, objective test situation, the concordance of the results with the validated "behavioral despair" test from Porsolt and the sensitivity to a wide range of drug doses.

PMID: 3923523 [PubMed - indexed for MEDLINE]

Related Links

The automated Tail Suspension Test: a computerized device which differentiates [Prog Neuropsychopharmacol Biol Psychiatry. 1987]

Adaptation of the tail suspension test to the rat. [J Pharmacol. 1986]

Anti-immobility activity of different antidepressant drugs using the tail suspension test in normal or [Fundam Clin Pharmacol. 1993]

The antidepressant-like effects of neurokinin NK1 receptor antagonists in a gerbil tail suspension tes [Behav Pharmacol. 2003]

Activity of litoxetine and other serotonin uptake inhibitors in the tail suspension test in mice. [Pharmacol Biochem Behav. 1992]

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EXHIBIT B: PAGE 1 OF 1

1: Neurosci Lett. 2006 Jun 12;400(3):203-7. Epub 2006 Apr 3.

Gene expression and association analysis of LIM (PDLIM5) in major depression.

Iga J, Ueno S, Yamauchi K, Numata S, Motoki I, Tayoshi S, Kinouchi S, Ohta K, Song H, Morita K, Rokutan K, Tanabe H, Sano A, Ohmori T.

Department of Psychiatry, Course of Integrated Brain Sciences, Medical Informatics, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto, Tokushima 770-8503, Japan.

LIM (PDLIM5) is a small protein that interacts with protein kinase C-epsilon and the N-type calcium channel alpha-1B subunit and modulates neuronal calcium signaling. Recently, the LIM mRNA expression in postmortem brains and immortalized lymphoblastoid cells from mood disorder patients was reported to be changed and seems to be involved in its pathophysiology. We hypothesized that the expression of the LIM mRNA in the native peripheral leukocytes may be a good candidate for the biological marker for mood disorders. Twenty patients with major depression and age- and sex-matched control subjects were included in this expression study. The LIM mRNA levels in the peripheral leukocytes from drug-naive depressive patients were significantly lower than those from control subjects and increased significantly after 4-week paroxetine treatments, to almost the same level as controls'. Hamilton depressive scores (HAM-D) were improved about 50% after 4-week treatment but neither paroxetine concentrations nor the changes of HAM-D scores showed significant correlation with the change of the mRNA levels. Then, we genotyped three single nucleotide polymorphic markers of LIM gene, which were reported to be associated with bipolar disorder in patients with major depression and control subjects (n=130, each), but there were no associations between these SNPs and major depression. Our investigation indicates that the lower expression levels of LIM mRNA in the peripheral leukocytes are associated with the depressive state and that its recovery after treatment may be an adaptive change induced by the antidepressant.

PMID: 16595163 [PubMed - indexed for MEDLINE]

Related Links

- Gene expression and association analyses of LIM (PDLIM5) in bipolar disorder and schizophrenia. [Mol Psychiatry. 2005]
- Gene expression and association analysis of vascular endothelial growth [Prog Neuropsychopharmacol Biol Psychiatry. 2007]
- Gene expression in the peripheral leukocytes and association analysis of PDLIM5 gene in schizophrenia. [Neurosci Lett. 2007]
- Serotonin transporter mRNA expression in peripheral leukocytes of patients with major depression before and after treatment with paroxetine. [Neurosci Lett. 2005]
- Combined treatment with sulpiride and paroxetine for accelerated response in patients with major depressive disorder. [J Clin Psychopharmacol. 2005]

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